President Northrop

A Theory of Somatic Equilibrium with Illustrations of a Possible Mechanism therefor in the Skin.

By C. L. HERRICK.

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LIFE.

Clarence Luther Herrick was born June 21st, 1858, in Minneapolis, Minnesota, in the public schools of which place he received his common-school education. He entered the University of Minnesota in the college year of 1877-1878 after several years in the preparatory department and was graduated in 1879-1880. He served a number of years as assistant upon the Geological Survey of the state in the capacity of natural history draughtsman, collector and, later, as mammologist. He also served as instructor in botany during his Junior year and as zoological instructor in the summer school, after graduation.

The season of 1881-82 was spent in special studies in Leipzig, where his instructors were Professors Leuckart, Chun, Rauber, Credner and others. Subsequently a winter was spent in Berlin under the guidance of Professors Fritsch, Benda, Ebbinghaus, Hertwig, Ramond and others.

He has served at various times on the geological surveys of Minnesota, Ohio, Canada, Alabama, and New Mexico. He was professor of geology and biology in Denison University from 1884 to 1889 and in the University of Cincinnati from 1889 to 1891, professor of biology in the University of Chicago during 1891-92, professor of biology in Denison University from 1892 to 1896, and president of the University of New Mexico from 1897 to date. He has been editor of the Journal of Comparative Neurology, Bulletins of Denison University and served for some years on the editorial staff of the American Geologist. His special studies have been neurology, comparative anatomy, histology, paleontology of the Carboniferous and petrography of the Lake Superior region. Minor studies were in micro-crustacea, mammalogy, ornithology and botany.

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No. 2.

PHYSIOLOGICAL COROLLARIES OF THE EQUILIBRIUM THEORY OF NERVOUS ACTION AND CONTROL.

By C. L. HERRICK.

Opportunity has afforded incidentally in connection with previous articles in this journal to point out the suggestions from anatomy in favor of a theory of nervous action based on the fundamental conception that the differentia of the various forms of nervous action consist in differences in the form of resistance and the reaction thereto, or, in other words, that nerve action partakes of the nature of equilibrium. It may now be permitted to offer fresh illustrations of the application of this principle. In the first place, however, we may note that in no department of physical science is it so plain as in neurology that we are dealing wholly with dynamic elements. While it is true that in the structure of the brain we have to do with morphological details of marvelous complexity and the descriptive side of our work is concerned with the varying outlines, sizes, and combinations of cells, fibres, etc., and the still more recondite structures within the cell and their dendrites, yet it is always obvious that these morphological peculiarities are but the expressions of inner forces and their responses to others from without. Thus it may even be doubted whether such a body as a centrosome or, at any rate, a centrosphere exists as a material element. Authors have been content to interpret the "asters" as the visual evidence of differential attraction in the cytoplasm.

It is possible to go farther and admit that all the structures with which the cytologist (and so the physiologist) has to deal are the visual interpretations of dynamic processes. This is more apparent to the neurologist than to the crystallographer because the former grows accustomed to observe the close correlation between structural differences and conscious experience whose dynamic nature it is impossible to doubt. There can be no more doubt that the morphological peculiarities of nervous or other tissue are the expression of the equilibrated forces of growth and other functions than that the form and polariscopic qualities of a crystal represent molecular reactions. It is also apparent that the concept of matter in either case helps not at all in the explanation of these forces and that the attribute of materiality is to be determined on independent grounds. Not to discuss the ontological question at this time, it may simply be said that in our use of the morphological terms it is only with the reservation that they are convenient expressions to define the constant elements in our experience of dynamic forms. There are many advantages in this more direct interpretation of vital phenomena, for by the interpolation of imaginary material elements between the objective force and the subjective experience one loses sight of the constant dynamism—a dynamism which does not make necessary a fresh explanation of each new expression of force; for the existence of force may be regarded as self-evident when we recall that activity is the sole element of experience, and its varying forms are, in a sense, the algebraic expressions for interactions. The whole question of trophism is robbed of most of its difficulties if we think of structure as not a thing dissimilar from function, but consider both as different expressions of similar forces.

It would seem that especially in the sphere of embryology we should be ready for the abandonment of the fruitless search for material grounds for persistence of type. The theory of pangens is one illustration out of many of the absurdities to which a materialist construction is driven. The observed conformity to type observed in each of the thousand plants which may arise by minute subdivision of a moss, for example, shows how hopeless is the attempt to base on any specific material the capacity for heredity, no matter how eked out by the doctrine of latency. Correspondence in mode is the condition of identity implied by a dynamic theory, and the heterogeneity expressed in the forces of the body of a man may be expressed in the terms of the forces of a spermatozoan equally well. The assimilative power necessary when we assume that repeated nucleary division takes place without reduction of the chromatin is certainly dynamic and why should this dynamic determinant be limited to some material element? Does not the body preserve its integrity in spite of the flux of its materials? Why should not the actual material of the nucleoplasm be in a similar flux while retaining its form, i. e., its dynamic attributes?

From this point of view the coordination of parts through the nervous system becomes only a special instance of a coordination in the entire organism. It is true that even the unexpected wealth of fibrous ramification in the nervous end-organs revealed by the various applications of the Golgi method is still insufficient to explain the perfect co-adjustment of part with part in nutritive and trophic equilibrium—in fact, *any* conceivable completeness of nervous *continua* would leave something to be explained, for, in the last analysis, the processes are intracellular or even cytoplasmic, Even if we should grant that unsuspected imperfections in our present methods deprive us of the power of detecting the anastomoses between neurocytes in the same circuit, yet the most perfect conceivable continuity would still leave an appeal lying to protoplasmic transmission. A forthcoming paper will afford illustrations of what is here referred to. In the skin of many (probably all) amphibia and reptiles (Axolotl and *Phrynosoma*) there exists about the cells of Leydig a very complete and beautiful protoplasmic reticulum in such a way that each large cell is completely enveloped, while the meshes commingle and pass from cell to cell. This reticulum arises from certain nucleated protoblasts which are devoid of cell wall and whose naked protoplasm fills in interstices between the larger cells. This reticulum is not an artifact for it is found by the use of widely different reagents and is most complete when the fixation of the protoplasmic structure is most perfect, and in some cases of applications of chrome-osmic + platinic chloride + alcohol solutions this perfection leaves little to be desired. Ordinary hardening processes do not reveal the structure as a rule. It may be that the protoplasm is a delicate film which is thicker in certain parts than in others but the relation to the intercellular nuclei is certain. These are entirely distinct from the chromatophores. Bethe's methylene blue process reveals the farther fact that nerve fibers, which lose the sheaths after passing through the corium, end in knob-like tuberosities in proximity to these nuclei, though whether they penetrate the protoplasm or simply spread out upon it remains, from the nature of the method, uncertain. These nerve-fibers when stained with picro carmine or fuchsin, in contrast to haematoxylin nucleary stains, seem to blend with the protoplasm and it is difficult to decide which appearance is nearer the truth. Such close contiguity between a naked fiber and a naked protoblast is too vaguely different from continuity to require physiological separation, however important the distinction may appear morphologically.

Here we have an illustration of a condition, which I believe is more general than we now can demonstrate, in which a nervous end-organ is so connected with a meshwork of vast extent as to suggest a very extensive somatic influence of a nature similar to nervous reaction over vast tissue areas.

We venture to suggest that there is no such sharp distinction between nervous functioning and the intracellular processes of the ordinary non-nervous cell as our present terminology and usage suggest. It is certain that in the differentiation of function the cells of the body at large do not give up all of their heritage of nervous or nerve-like power. Students of histogenesis may have been puzzled, as the writer has, to account for the fact that a very remarkable degree of coordinated trophic power is exhibed by the embryonic body prior to the development of nerve tracts and end-organs. The phenomena of nervous deficiency in anencephalic monsters is equally inexplicaple from the standpoint of rigid limitation of coordinating power to the nervous system. In the sponges and Cœlenterata it is plain that the coordination necessary to individual existence and perpetuation of specific characters is possible with no central nervous system. There is a form of vital equilibrium so resident in the general system as to give rise to much the same phenomena of nervous unity as in the case of higher animals. It is not at all necessary to suppose that the cells of the body of higher animals have lost this power during the differentiation of the central system ; it would be more probable that the central system should be superadded.

There are a number of classes of cells which seem to be, in the nature of the case, freed from all direct nervous control. The chromatophores of the Amphibia, to which the writer has devoted some study, seem in some cases not to be in a direct way associated with a definite nervous supply.[1] They are, indeed, literary migratory, though the scope and range of movement remains to be worked out. Two things may be quite positively stated ; first, that these cells are to some extent independent of fixed nervous influence, and, second, that they are very really under indirect nervous control. Experiments tried in my laboratory many years ago showed that, in young cat fish, section of a branch of one of the cranial nerves destroyed the very marked adaptive power for the injured side. A fish, originally black, when placed in an aquarium with yellow bottom invariably changed to the color of the environment unless the mutilation described prevented it.

The observations of G. H. Parker on photometric changes in retinal pigment cells of *Palæmonetes* are interesting in this connection in showing that exposure to light causes actual changes in form and a segregation of the pigment of these cells. He finds that section of the nerve or severing the eye stalk from the body does not wholly prevent the reaction. This is an illustration of a reaction exceedingly resembling a true nervous response.

The embryonic tissues of all animals possess this coordinating sensitiveness and trophic interaction to a high degree. In the extreme case afforded by the blood corpuscles and lymphocytes it seems perfectly plain that there can be no direct

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[1] Methylene blue seems to show connections in some instances.

nervous relation and yet he would be a bold physiologist who would venture to deny that there is a most subtle and powerful coordination between the stationary tissues and the free corpuscles. One may talk of chemotropism or vital susceptibility, but such terms express merely the fact that the corpuscles, like other cells, are coordinated with the rest of the body and bear both its specific and individual impress. The mysteries of serum therapy only increase our confidence in such an intimate relation.

It, then, may be supposed that the circuit of nervous action in any part of the body passes through a variety of smaller somatic circuits and that the spheres of the two forms of activity overlap so that the return nerve current bears the influence of this interaction. The nervous equilibrium is only a central specialized part of a vital equilibrium embracing all the activities of the body. The wandering cell, even though not in direct continuity with a nerve fiber, nevertheless may be said to act in a "nervous field" and so is not beyond the sphere of coordination, while, on the other hand, the results of changes in the extra-nervous mechanism of the body all have their effect upon the central system. In the same way we may explain the effect of the sum of organic and total or somatic stimuli upon temperament and disposition.

The processes of nutrition may be said to be common to protoplasm quite irrespective of nervous control, but the trophic influence of the latter is well authenticated and it may be assumed that no nervous action takes place without having its effect on growth. From the above it may be gathered that the ground of the mutual reaction may be sought in the fundamental similarity of the two processes, or rather the close relation between the processes of waste and repair lying at the foundation of both. It is necessary to suppose, accordingly, that the central nervous system is continually affected by the vital phenomena of the body at large as truly as the vascular system is under the control of the nervous system.

As a striking result of this effect of the somatic or extraneural processes, one may take the phenomena connected with the restoration of mutilations. When the newt's foot is amputated, under favorable circumstances the organ is quickly reproduced and the parts so restored differ in no obvious way from the old organ removed. What is the power which causes such a miraculous change? Does it take place because a simulacrum of the missing limb exists in the soul and the new body develops to correspond? With due allowance for use of terms, we reply, "yes, such a simulacrum does exist." The form of the central equilibrium has been determined by constant reactions between the member and the central system and when the member is lost the equilibrium so established is still in force and the nervous stimuli which but lately served to supply tone to the limb now operate upon the stump. Intense irritation results and the tendency is to influence growth at the point of injury.[1] This growth is under the directive control of the nerve just as we know the normal growth constantly to be. If the nerve of the limb be injured beyond repair monstrous growth results. It may be assumed that in case the leg were amputated and the nerve destroyed in the stump above, that the efforts at restoration might be abortive or result in monstrosities. It would be well to test this matter experimentally. It is believed that the application of the ideas indicated in this paper to the higher spheres of nervous activity will prove fruitful.

Another application of the same principle is found in the processes connected with the regeneration of severed nerves. It is a well authenticated fact that, in the case of section of a peripheral nerve, the nuclei of the sheath of Schwann pass to the centre of the lumen and form the protoplasmic prota of the segments of the new nerve—a process wholly unintelligible if we agree with Kölliker in regarding the sheath nuclei as derived from non-nervous connective tissue corpuscles, but not so remarkable if the abundant evidence be accepted that these nuclei are but the diverted nuclei of the cells which formed the nerve

[1] The assumption that irritation may produce proliferation is supported by the pathological karyokinesis in case of local irritation; see also processes connected with development of spermatozoids, etc.

originally by proliferation and moniliform concrescesce.[1] We here have an instance where the protoplasm of the cells has become specialized and the nuclei switched out of the circuit and apparently related to the process of forming the cell wall. But, in spite of the specialization implied in the production of an organ for nervous conveyance alone, it appears that the early nature of the cells is dormant rather than lost, so that in the case of injury and the consequent degeneration of the myelin and axis cylinder, the nuclei, with the small portion of less specialized protoplasm associated, return to the embryonic state and repeat the process of neuro-proliferation, after which the new channel is organized from the center outward and the nuclei return to their parietal position. It is more than probable that a similar rejuvenescence is possible in the case of other tissues also.

We have many instances of the same kind of differentiation within the cell. Take as an illustration the formation of glands in the skin of the frog, where a follicle is formed and then the several component cells are fused, the outlines being lost, and only the small nuclei which remain in the thin parietal layer of less altered protoplasm remain to indicate that the gland is really polycellular. It would be interesting in this case to institute experiments on the possibility of rejuvenescence of such cells.

In the application of the neural equilibrium theory to problems of heredity it would seem that there is a large and profitable field. Without attempting details in this direction, it may be pointed out that this point of approach renders unnecessary a vast deal of the most profitless theorizing in reference to heredity. If the neural and somatic forms of reaction are not absolutely unlike, but on the contrary are parts of a common vital type of energy (or rather force) and if it be admitted that the processes of nutrition may be and are influenced by the

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[1] The nuclei of the ending of the motor nerve on the muscle offer interesting collateral evidence. See the article by Dr. Huber in the last number of this Journal

neural equilibrium, it follows that the germ is also situated in the field of these equilibrated forces and its composition, i. e. its own force formula, would be the resultant of the reaction of the existing (ontogenetic) formula as modifying the earlier (phylogenetic) force formula. Instead, then, of searching for "ids," "bioplasts," gemmules," or the like we may feel assured that, in a much more complete and integrated form, the entire life of the organism will have its effect on the germ. This confidence will not cause us to pay less attention to the structural appearance of the cell and, in particular, the germ cells, but will prevent loss of valuable effort in the invention of sterile theories and prepare the way for a dynamic interpretation of these phenomena.

It may be noted in this connection that S. Ramon y Cajal has apparently suggested, by implicatian at least, some of the grounds for the equilibrium theory in his suggestive article in the *Archiv f. Anatomie u. Physiologie*, 1895. He says: "Die Phänomen der vorerwähnten lawinenartigen Leitung, sowie die geringe Zahl der sensorischen Elemente (Zapfen der Fovea centralis, akustische Zellen u. s. w.) welche alle die zahlreichen Eindrücke, für welche unsere Sinne empfänglich sind, aufnehmen müssen, zwingen zu der Annahme dass jede Sinneszelle, sowie jede subordinirte Gruppe von Pyramidenzellen des Gehirns successiv an der Production verschiedener Bilder sich betheiligen. Vom anatomisch-physiologishen Standpunkt aus, wird eine Wahrnehmung von einanderen, zu derselben Empfindungsquantität gehörigen, durch die Zahl und die betreffende Lage der corticalen in Erregung gesetzten Pyramidengruppen unterscheiden." It would seem to be evident from the above that not only the exact impression to be perceived is not produced by the organ of sense (since it would then be divided into a large number of parts in being transferred to the larger number of pyramid cells) but also that inasmuch as the same cells may be participants in different percepts the physiological basis for the latter must be the particular formula of these permutations in a given case and thus a simple impression must be of the nature of an equilibrium constructed from the interactions of the cells implicated.

In conclusion, it may be noticed that the ideas advocated above have a very interesting bearing on the problem of the origin of variation. The theory of the competition of parts has taken strong hold of modern biology because it is becoming more and more evident that the sphere of natural selection must be greatly restricted and some appeal must be made to forces residing within the organism. Even Weismann in his extreme advocacy of natural selection has been forced to yield a large place to the effects of inner coordinations. We suggest that the nature of these coordinations is rendered much more intelligible by conceiving of all these vital-nutritive processes as equilibrated forces. If for any reason, a given part or tissue of the body is in the least exaggerated, its part in this complex coordination is increased and, accordingly, its reflex influence on the organism as a whole, or its nerve centers, will be increased and its quantum of the centrifugal currents will also be increased, so that the tendency will manifestly be for the newly created variation to go on increasing indefinitely until checked. The next generation will inherit this tendency and we should find that, in the absence of restraint, there would be the constant likelihood of the appearances of strange monstrosities with apparently unaccountable exaggerations of horn or spine. It requires very little familiarity with paleontology to discover that its records abound with cases in which no possible serviceability would account for the absurd burlesques which have been produced and only the comparative familiarity of existing types blinds us to the same fact. While not denying that there is a large element of useful adaptation in all cases (otherwise they would never have been preserved), yet it will be admitted that a very considerable proportion of the peculiarities and often the deeper seated characters have no such explanation. We should not be surprised at this, for it is apparent that the slightest variation not directly hurtful will tend to perpetuate itself. It may be said that all unnecessary parts will be eliminated as sapping the nutrition of the body at large. This is an abuse of a teleological principle for it is not to be assumed that the body is reasoning from present causes to distant effects. If an eye ceases to be used it is atrophied, not because it is no longer useful and is therefore a cumberer of the ground, but because, the function having ceased, it is actually participating less in the equilibrium than formerly and also less than other organs. But a newly formly wart on the skin may be absolutely useless, yet, like a corn, it may be the seat of irritative processes which stimulate nutrition. It is then not the ideal utility but the degree of participation in the vital equilibrium which is the primary determinant. It is necessary to seek no farther for the source of variation and it is not surprising, when we consider the infinite possibilities for the increased vital activity of one group of cells over another that natural mimicry has found at hand all the necessary variations upon which it is to work, though we must not hope to find in their number and variety the complete explanations of the imitations produced.

University of New Mexico, Feb. 20th, 1898.

The Somatic Equilibrium and the Nerve Endings in the Skin.

Few problems have proven more attractive or more illusory than the general question as to the nature of the nerve termini in the membranes, for it would seem that our concepts of the histogenesis and so of the real nature of the sense organs depend very largely upon the conclusion at which we arrive as to the relation between the various types of sensory epithelium. The writer suggested, in a series of papers on the brain of the lower vertebrates, reasons for believing that the first sense to come into the field of consciousness was that of smell, and a little later Edinger emphasized the same idea by his investigations of the olfactory tracts of the reptile brain. It may now be taken as fairly proven that, if the seat of consciousness is in the cerebrum, smell was the first of the special senses to find its way to recognition by it. It would then be natural that we should expect the peripheral organs of olfaction to retain a primitive character and so to afford us a clue to the early state of such organs. Then too the development of the accessory or non-nervous organs of sense has here hardly made any progress even in those most highly differentiated cases in which Jacobson's organ has assumed great proportions.

From studies of the development of the olfactory organs in reptiles, as reported briefly in earlier numbers of this Journal, the writer has been abundantly convinced of the truth of Beard's statement that the olfactory prota arise from the skin and, by a

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It should be stated that the writer has received material assistance in the preparation of the slides upon which this and the following paragraphs are based from members of his classes in the University of New Mexico and particularly from Mr. George E. Coghill, Fellow in Biology. The responsibility for the results here offered is wholly with the writer.

proliferation, extend to the brain, there to enter into communication in the glomerules with the processes of the mitral cells of the tuber.

As studied in the embryos of snakes the process is as follows: The first indication of the change of the ordinary to the sensory epithelium is seen in the thickening of a portion of the superficial layer from the morphological front of the head (the region of the future infundibular recess) in relatively broad bands, one on either side of the head. As the head flexures increase, these areas are carried ventrad and come to occupy the roof of the mouth and adjacent parts of the buccal cavity. The development of the taste buds from this epithelium we have not traced in these subjects, though there is no reason to doubt that they are formed from this proton, as it is easy to see that the mucous part of the hypophysis is. At the time the first olfactory rudiments appear, the curvature is such that the hemispheres are protuberant in front and so come nearly in contact with the prota of the olfactory in the two bands of germinative epithelium above mentioned. Still there is no difficulty in seeing that the original proliferations take place in the skin and that the constant proliferation by division of the earlier cells spins the nerve fiber from the original source to the point where the tuber subsequently arises. In fact, the tuber, which has frequently been compared to the ganglion of origin of a cranial nerve, does not seem to afford origin for any centrifugal fibers whatever. In preparations by the silver method it is easy to see that the neurite of the moniliform chain of the olfactory nerve comes into relations in the glomerules with dendrites of the mitral cells. Though a considerable wealth of detail has been secured by study of Golgi preparations during the last few years, nothing has been brought to light to invalidate our original view.

For a long time during the development of the brain an obvious ganglionic mass lies below the skin at the base of the point of origin of the olfactory. The gradual elaboration of the cavities of the nares only serves to redistribute the prota without materially disturbing the simplicity of the arrangement.

In a wide range of types it has been possible to make out the adult conditions which have often been correctly described. Merkel in his classical work gives a figure of sensory endings from a cirrus of Amphioxus that compares in every detail with the specific cells of the olfactory epithelium of a reptile or amphibian. (Plate III, figure 10.) Few if any of those who have studied the development of the olfactory will venture to deny that the "Stiftzelle" at the peripheral end of the olfactory nerve is a member of the nervous series having the same origin, though it is doubless conceivable that, through some strange fatality, every observer has failed to notice the intrusion of a foreign element at some stage of the process. (Fig. 31.) If, however, we take for granted that the fiber is continuous, we claim that there is an equal necessity for admitting the same for other clusters of nerve endings on the surface of the body.

Although there was for a long time considerable disagreement as to the actual connections of the olfactory nerve fibers, and the classical studies of Kölliker, Klein and Piana left the matter open, it seems as though the later studies of Ehrlich, Arnstein, Cajal, Gehucten, Retzius, Brunn and Lenhossèk, who employed the silver and methylene blue methods, were sufficient to prove conclusively that the olfactory epithelium possesses rod cells whose proximal end is an actual continuity with the fiber of an olfactory nerve filament. The writer has frequently verified this in specimens of Amphibia double stained with hæmatoxylin and picrocarmine in which very unambiguous views can be secured. A few figures from these preparations were published by Mr. Bawden, then a student in the writer's laboratory (Jour. Comp. Neurol. IV). Our studies in the development of the olfactory nerve show that the proton of the nerve is formed in or under the epithelium of the nasal area and that the nerve grows by moniliform concrescence of cells which arise by mitosis from this proton. From this stand-point, then, it would be expected that the neurocytes of origin would be found in the epithelium. In all essential respects the relations in Jacobson's organ are the same as in the true nasal olfactory epithelium. The accompanying figure (Plate V, Fig. 10) from an article by Lenhossèk (Anatom. Anzeiger, VII, 19-20.) illustrates these conditions and also the fact that other nerve fibers, apparently from the trigeminus, terminate in free arborizations between the epithelium cells. A very large following of the new school are prepared to claim that the conditions in the olfactory epithelium are peculiar to it alone and it is even attempted to correlate this with a supposed fundamental difference in origin and structure of the olfactory from all other nerves of the body. But we are able to show that in the epidermal sense buds of the tree frog and other amphibia the same continuity of nerve fiber and cell can be determined.

It has not been an altogether unnatural result of the remarkable complications of nervous structure revealed by the so-called specific methods that the results obtained by the old histological methods have been discredited and it has required some year's experience to teach us the danger of too explicit reliance on the former. Perhaps the greatest of these sources of ambiguity arises simply from the fact that has been regarded as the chief excellence of these methods, namely that the selection is so perfect that other tissues than those selected not shown at all or, even if the after-staining of sections succeeds, the conditions of impregnation are so unlike that the tracing of connections or definite relations is difficult or impossible. The absolutely contrary results of Dogiel and Cajal in the matter of the anastomoses in the retina illustrate the difficulty that exists even where the methods used are similar. The results of our own studies are rather to confirm many of the old observations and to show that there are two distinct classes of dermal endings. Of these the olfactory illustrates one and the most primitive one. In this case we have to deal with the remnants of nervous aggregates which were originally formed in or near the outer layer and in the phylogenetic development have not been diverted to a deeper level as is true in so many other instances.

In our laboratory in 1891 we made out the fact that in the oral region of the earth-worm there are cells in the skin which have a nervous nature and whose processes pass entad to the central system. Owing to a delay in the other aspects of the research the observation was not made public till the brilliant work of Gehuchten had afforded proof of the same thing, but the suggestion was of course inevitable that we have in the lower forms a permanent retention of cells in the skin which in higher types have tended to become concentrated in the central organs. What more natural, however, than that this concentration should be incomplete, especially where these cells have have acquired a specific sensory function. When the application of the Golgi and methylene blue methods revealed the fact that there is a most complicated set of free endings in the skin and that in many cases where a nervous continuity had been described there is simply a secondary apposition of a dendrite to preexisting non-nervous cells it was inevitable that the existence of cellular nerve endings should be discredited entirely. It is true that the greater part of the sensory prota are collected in the spinal and cranial ganglia and seem to proliferate thence to the periphery; but in various regions, particularly of the head, these ganglia never concentrate in a neural ridge but retain their original place in the neighborhood of pharyngeal clefts and the like and the possibility must be allowed that other cell-clusters elsewhere may have done the same. However, there is another possibility to be considered; namely, that the terminal portion of the peripherally proliferating nerve fiber may under certain circumstances develop a specialized terminal dendrite. When the nerve is in process of developing the subdivision of the distal member is repeated progressively until the definite terminus is reached and then the extreme element is charged with the function of adapting itself to the conditions there prevailing. In the case of the motor ending, even the careful researches of Huber and De Witt do not finally dispose of the question as to the origin of the end-structures. We may interpret them as follows: when the fiber reaches the muscle its terminal element, together with the nucleus, applies itself to the surface of the latter and prior to the formation of the muscle-sheath, proliferation goes on in a less regular way than during the development of the nerve itself, in this way is formed the "sole," which would, accordingly, be of a nervous nature. On the other hand, it is possible that the nerve on entering the muscle comes in contact with a nucleus of the muscle which, under the stimulus afforded, begins to proliferate and the protoplasm of the cells so formed assumes an intermediary character and spreads out upon the surface of the muscular band as a means of applying the stimulation. To us the first is in the absence of direct evidence the more probable solution.

Observations are at hand which tend to show that extensive nervous proliferation takes place below the corium of the skin at an early stage. In section of the skin of Amphibia these proliferating cells can be seen and this is probably the origin of the ganglion plexus of the skin. (Figs. 3, 5 and 6, Plate V.)

To pass then to the nerve endings in the skin, we may first note the isolated sensory cells. These may be seen in suitably prepared sections of the head in the tree frog and other Anura and also in the neighborhood of the eye in the axolotl and other tailed Amphibia. In the tree frog, where they most numerous, these cells are grouped in threes and fours in close clustres lying in a special cavity passing through the entire thickness of the epithelial layer. The terminal segment is a slender nucleated cell, the nucleus being very narrow. The peripheral part of the cell is a narrow rod which at the periphery bears a few rigid bristles. Entally from the nucleus the cell walls are very delicate but obvious and the nerve fiber within is easily distinguishable in the doubly stained specimens. The fiber is easily followed to the corium layer and in many cases through it. It seems too that more than one nucleus can be seen in the course of the fiber before the passage through the corium. The skin is at this point very thick and the presence of large glands serves to separate the corium from the epithelial layer, so that the course of these fibers is readily followed for a long distance. In the case of certain teased preparations it was possible to isolate these fibers and study them with oil immersions and there can be no doubt as to the relations here described. So far as could be told, these fibers do not connect with the subepithelial plexus as do the fibers of the free arborizations to be described later. (Figs. 2, 12, 13, 14.) The terminal segment seems to be entirely homologous with the segments of the nerve and its peripheral portion is perhaps simply a modified dendrite.

The endings above described must not be confused with the sense buds found elsewhere in the skin. In the latter there is a well-developed accessory apparatus in the form of the well-known beaker or "Stutz" cells, here there is simply a cavity or tube in the midst of unmodified epithelium cells. Yet it is not to be assumed without better evidence than is now at command that these two classes are of entirely distinct nature and origin. In the first place it is scarcely to be credited that two sets of sensory organs derived from the same proton and so similar in function as are the organs of smell and taste should be of an absolutely different type, and what may be said of the taste buds applies *mutatis mutandis* to the sensory buds of the skin.

The contrast between the results of different methods is nowhere better illustrated than in the different conclusions reached by Fusari and Panasci on the one hand (Arch. italiennes de Biol. XIV, p. 240) and those of Arnstein (Archiv f. mikroskop. Anat. XXXXI, 2). The former authors worked with the chrome-silver method and describe a direct communication of the nerve fiber with the axial (rod) cells of the taste buds. (This we are able to substantiate from personal observation.) Arnstein, on the other hand, denies such connection most emphatically and claims that teased preparations with methylene blue show with all possible clearness that there is no such connection, but instead that the varicose nerve fibers form a felting of fibers around the axial and outer cells of the bud and end free in the pore. Arnstein finds quite similar nerve endings in the filiform papillæ. He does not find forked cells, but inclines to the view that such cells result from the separation of the true nerve fiber from the peripheral end of the cell to which it is attached. The appearance of continuity between the cell and the nerve fiber is said to be illusory and is explained as due to the blackening of the cell as well as the fiber. Ehrlich (Deutsch. med. Wochenschrift, 1886, 4) described intensely colored cells in the mucous membrane of the olfactory region which pass without interruption into a nerve fiber, but these cases Arnstein also dismisses as illusory. Dr. Niemack has also reached similar conclusions by the use of different material (Anat. Heften, Merkel und Bonnet, Anat. Anzeiger, VIII, p. 20.)

Inasmuch as the epithelial layers of the mouth and tongue are morphologically only portions of the skin, it is necessary to examine these regions for light on the nerve endings as they may be modified under the special conditions here existing. In the frog, which has been the subject of the most elaborate invstigation, the sense of taste cannot be at all highly developed, for the animal is accustomed to swallow its food, chiefly horny coated insects, without mastication; and experiments (Bethe) prove a very sluggish response to chemical irritants. In the tongue of the frog, as well as in the palate, there are numerous scattered specific sense organs, those of the tongue being flat end-plates, while those of the palate are protuberant sensory papillae. Athough these organs were described by Leydig in 1858 they have frequently been the objects of special study since then and even now authors are not wholly in agreement as to the details of the structure. The cellular elements in these sense organs consist of the cylinder of flask cells forming the protection for the sensory rod cells, a subordinate variety of which has been termed forked cells by reason of the divided peripheral projection. Alate, or winged cells, around the cup or flask have also been noticed by some authors. Bethe, who has recently studied these buds by means of the modification of the methylene blue method which bears his name, finds two sorts of nervous termini in them: first, free termini lying between the cylinder cells and reaching the surface, second termini with bulb-like expansions on various cells. (Fig. 8.) One type of such endings is three-lobed and such endings are affixed to the sides of the cylinder cells; the other variety has simple circular end-plates and these endings are found on the rod cells, fork-cells and possibly also on cylinder cells. In no case did Bethe succeed in finding actual continuity between the rod-cells and the nerve. He in fact seems to find greater intimacy of connection between the cylinder cells, which are not supposed to have a nervous function, than with the rod-cells and in no case is there more than a contact with the cell wall. He explains the continuity detected by Arnstein and others as the result of faulty observation and imperfect methods. In the ordinary pavement epithelium of the palate Bethe finds termini on gland cells and ciliated cells, as well as deeper elements. It should be noted that the finding of the three-lobed end-plates on the cylinder cells was not a uniform occurrence but rather exceptional and the suggestion is near that this is the result of an accidental state of the fibers and not a natural or permanent organ.

Our own studies of the gustatory epithelium of the axolotle are in accord with the results of Bethe upon the frog so far as the diffuse endings are concerned, though the methylene blue does not give adequate insight into the connections between fibers and cells. The taste buds, on the other hand, afford similar results to those obtained from the sensory buds of the skin. The source of many of the erroneous conclusions reached is, as mentioned beyond, the fact that in successful methylene blue preparations it often happens that fibrous elements stain when the cells of origin for the same fibers do not.

Diffuse Peripheral Connections.—Various early writers have reported the existence of a dense net-work or felting of nervous material among the epithelial and even the corneum cells of the skin. This structure was first made out by the use of gold chloride and there was always left open the possibility that the appearance was due to the disposition of metallic salts in the interstices between the cells. Dogiel in his paper on the nerve endings of the genitalia figures a very extensive mesh-work of this kind with here and there a free knob-like termination and he traces the lower part of the reticulum to a direct communication with a set of nerve fibers passing perpendicular to the skin. (Fig. 1.) Strong in his paper on the cranial nerves of the frog figures a similarly minute meshwork which is revealed in this case by the use of the Golgi method. In all of the above cases there is the element of uncertainty growing out of the fact that the methods are impregnation rather than staining processes and are histologically uncertain. It would then be eminently desirable to supplement the evidence from these sources by other means. In the study of the skin of the Amphibia it is easily noted that there exists at the base or ental aspect of the layer of Malpighi a layer or stratum which is in a peculiarly nascent state. These cells are devoid of the thick and rigid walls chatacteristic of the superficial cells and are protoblasts rather than complete cells. In this layer we may find, at all stages, the evidences of mitotic division. In fact there is a permanent proliferating zone in this region. Comparison of this stratum with that of higher vertebrates shows that the latter form no exception, though it is not always easy to detect the protoblastic elements. A single theoretical consideration is sufficient to convince one that this is what should be expected, for it is of course recognized that every type of vertebrate has some provision for the constant or occasional removal of the skin. In some cases the process of removal of the corneum is intermittent, while in others it is gradual. In either case it is obvious that there must be a proton of undifferentiated material—of cells that have not passed beyond the plastic stage. In those parts of the skin where there is little differentiation between the various layers the difference between the corneum and deeper cells is not readily detected in preparations by the usual processes, but in the thicker portions where the so-called Leydig cells appear the basal protoblasts are crowded into the interspaces and pried apart. One effect of this process has been to stretch the connecting protoplasm into an excessively thin layer or film enveloping the Leydig cell either completely or as a coarse mesh-work of naked protoplasm. In all the preparations we have seen, even those in which the preservation has been as perfect as possible, without the least evidence of shrinkage, the appearance is that of a broad reticulum arising in the intercallary or basal protoblasts and enveloping the cell in such a way as to wrap it completely in the products of the adjacent protoblasts. The most perfect process of preservation for such structures is a combination of chrom-acetic and platinic chloride diluted in alcohol. The use of Merkel's solution also gave very good results, while the various osmic acid solutions invariably produce too great shrinkage of some parts, especially of the reticulum. In the first mentioned solution it appears that the natural tendencies of the alcohol and the chromic acid counteract each other while the fixing action of the platinic chloride is in no way interfered with. The avidity to all the usual stains after this treatment is also very great, while in the osmic preparations there is not only general diminution of the receptivity, but, what is worse, the effect is not uniform even in the same class of tissue in the same preparation. In properly prepared sections the reticular structure of the protoplasm of the Leydig cells is most beautful, but when osmic solutions are used the contents of the vesicles is blackened and the result is a granular appearance instead. The pericellular mesh-work is stained red by picrocarmine, as is all protoplasmic matter, while the nuclei are all selected by the hæmatoxylin. Nerve fibers stain red but their nuclei are purple. The nerve supply is abundant and the fibers can be traced without difficulty through the corium layer in all preparations. The sheaths seem to cease after passing the corium and the subsequent course is less easy to make out. In a considerale number of cases it has been possible to trace such fibers with all desirable clearness to actual connection with the bases of the lower protoblasts above mentioned. The fiber is red, as is the protoplasm, so that it remains possible that the exact nature of the union is not obvious, yet from the fact that two masses of naked protoplasm thus come in contact, the range for possible modes of union cannot be extensive. In any case the most careful examination under immersion lenses of well-stained specimens does not reveal any form of intermedation between the fiber and the protoplasm of the cell. Nor is this relation limited to the lowest layer of protoblasts alone, for it is possible to trace fibers to some of the higher members as well. The attempt has repeatedly been been made to count the number of fibers entering the given area and then to compare this number with the number of protoblasts in the same area, with the result that the fibers proved more numerous than the cells in the lower series, thus offering independent evidence to the effect that these fibers are destined to more than the single basal row of protoblasts.

The pericellular net-work has been described by a number of the earlier observers, but in each case the real nature of the structure has not been detected. Paulicki and Pfitzner both regarded it as a mesh-like thickening of the cell wall. The latter thinks these "ribs" serve for the point of attachment of the "intercellular bridges." Part of Paulicki's description is given in full. "An einigen Leydig'schen Zellen wurde ich auf kleine kreisförmige, länzende, dunkelconturirte Figuren aufmerksam, die in ziemlich regelmässigen Abständen von einander entfernt der äusseren Fläche der zellmembran aufsassen. Es stellte sich nun alsbald heraus, das dieser Befund bei allen Leidig'schen Zellen ein ganz constanter ist. Ueber die Deutung dieser Gebilde erhielt ich durch Zellen, wie deren mehrere abgebildet sind, Aufschuss. Hier fand sich ein doupltconturirtes Gitterwerk, welches uber die Protoplasmakörner hinwegging. Die Balken des Gitterwerks theilten sich öfters gabelformig und waren bald dünner, bald dicker. Es ist nun anzunehmen, dass das Gitterwerk hervorgebracht wird durch rippenartige, partielle Verdickungen der Zellenmembran, und dass bei solchen Zellen, wo ein derartiges Gitterwerk zu sehen ist, der Schnitt die Zelle tangential getroffen hat, während bei den Zellen, die dieses Gitterwerk nicht zeigen, die dagegen in der Zellmembran von Strcek zu Streck kleine, glänzenden Ringe besitzen, der Schnitt mitten durch die Zelle gegangen ist. Die kleinen Kreise, die der Zellenmenbran aufsitzen, stellen die Querschnitte der rippenartigen Verdickungen der Membran dar. Die rippenartigen Verdickungen der Zellenmembran Zeigen sich durchs ämmtliche Farbemittel ebenso gefarbt, wie das Protoplasma, wesshalb sie leicht ubersehen werden könen." The author also notices that these bands are sometimes sharply stained by fuchsin, a fact that, in connection with the above, might well have suggested that these supposed ridges on the cell wall have a nature more in common with that of protoplasm. Still more suggestive was the additional observation that these ridges are not limited to any single cell, but often pass to neighboring cells without interruption. He says "Ich sah, dass die Balken von einer Leydig'scher Zelle continuirlich zusammenhingen mit den Balken benachbarter Leydig'scher Zellen, dass ein zusammenhängendes Balkenwerk sich uber mehere Leydig'sche Zellen ausdehnte. Ausserdam sah ich aber auch, dass ganz ähnlich gestaltete Balken sich auf die benachbarten Epithelzellen fortsetzen."

Our observations leave no doubt that this meshwork is not only of a protoplasmic nature but that the meshes are connected with the nuclei of the basal and intercallary series. (Figs. 17-20). It is easy to trace the meshes into communication with the proplasm surrounding these protoblasts. It is more difficult, except in the case of perfectly preserved material, to follow the nerve fibers to the bases of the cells of the higher series, i. e., those about the sides and ectad of the Leydig cells. In good methylene blue specimens stained *intra vitam* (Figs. 21-23), the fibers can be traced for a considerable distance into the epithelial layer among the intercallary nuclei, but it is only in specimens stained with picrocarmine and hæmatoxylin that the actual connection with the cells can be made out. Even here the question (always left wholly undecided by the methylene blue method) as to the nature of the association is not entirely deprived of its ambiguity. When a fiber of naked nerve-plasm unites with a protoblast of naked cytoplasm, who shall say whether the connection is primary or secondary in the absence of the most intimate embryological evidence or regeneration experiments?

An important question in this connection is that as to the source of the nerve fibers. Do they arise in the prota of the skin or do they enter the skin from out-growths of the spinal ganglia? It would seem natural to conclude that the latter is the case, and yet it is not a little puzzling to see that nearly every cell in this series has its fiber. Then, too, the fact has been repeatedly observed that the protoblasts are continually dividing, even in rather large specimens of axolotl. (Fig. 20). It must be left to careful embryological studies to decide whether there are cells of origin in the skin for centripetal nerves or not. Another question must await either an embryological or pathological solution, and that is the detection of centrifugal fibers among those entering the skin. Such non-medullated fibers doubtless occur and we may think of the plexus immediately below the epithelium is the probable site.

We have sought to verify the results above described by the application of the methylene blue *intra vitam* method as well as the tissue methods used by Dogiel, Bethe and Huber. Making all due allowance for the ambiguity of these methods, it seems that the results are in harmony with those above mentioned. It is not difficult to secure impregnations in which every fiber is stained throughout its course through the corium, but to our surprise they seemed to stop short in the vast majority of cases in the zone at the base of the layer of protoblasts, while only in comparatively few cases did we trace connections like those described by Bethe with cells of higher layers. In the chromatophore zone just ectad of the corium in many parts of the skin it was possible to trace fibers horizontally long distances and in some cases supposed communications with the chromatophores or similar bodies were noted. (Fig. 21). In most cases these cells were nearly destitute of pigment and pass by all gradations into undoubted ganglion cells.

In this connection mention should be made of the remarkable results reported by Dr. W. Pfitzner.[1] This writer claims to trace the fibers after their passage through the corium into the substance of the cells and to follow them to small knob-like endings free in the protoplasm of the cells. More than this, he traces to each cell, not only of the deeper layers but also of the stratum corneum, two independent fibers from quite distinct sources and founds upon this observation an elaborate hypothesis, which unfortunately is deprived of all standing-room by the evidence now at hand. Mr. Massie has pointed out that there is a stage in the young amphibian skin when a curious skein of a material staining deeply with some reagents is found in the cells. The senior writer, who made the preparations used by Mr. Massie, can vouch for the accuracy of this observation. It is not unlikely that the suggestion is waranted that this skein is an embryonic and transitory element in the development of gland cells, as it is not found in all the cells but in a certain class dispersed among narrower cells having a different reaction. This skein (Fig. 4) is as certainly intracellular as the nerve fibers are extracellular in their course. Figures almost identical with those published by Pfitzner as the results of his observation can be secured by his methods, especially if the sections are taken a little oblique (Fig. 24.) The process serves to stain very distinctly the part of the nerve that is medullated, i. e. that part extending through the corium, but not that part which extends

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[1] Nervenengungen im Epithel. *Morphol. Jahrbuch*, 1882, p. 726.

above the corium among the cells. Such fibers can be seen, it is true, but they are so different in appearance from the medullated part of these fibers that we are forced to conclude that what Dr. Pfitzner really saw is the intracellular skein of which mention has been made. It is a most natural mistake in the absence of more reliable methods and especially as the methylene blue process was not at his disposal. The finding of two nerve termini in each cell is apparently to be explained as a result of the fact that the base of the skein is hidden, as we found it to be in oblique or thick sections, so that the appearance figured by Pfitzner frequently recurs and if one had a preconception in favor of the the nervous structure of the element one might easily construe it as he has done. After the above we may be released from the obligation to consider the extensive and interesting theories based upon the supposed intracellular endings.

Transitional Cells. In certain regions of the skin the epithelium layer is greatly thickened and the Leydig cells are rereduced in number or carried to a higher (ectal) level. In such portions of the skin, as on the dorsal region, an interesting modification of the structure above described is found. Here the lower series of cells is elongated in a direction perpendicular to the surface forming a sort of palisade type of cells. A definite wall is often apparent in the lower portion proximad of the nucleus, while the peripheral part seems to fray out into a representative of the pericellular mesh-work. Where the Leydig cells are present there is every reason to believe that these cells participate in the formation of such of a pericellular network as has been described above but somewhat modified by the changed conditions. In a large number of cases we have observed a nerve fiber after passing through the corium seeking the base of these cells and making an intimate connection with one of them. Here the opportunity to observe the union is much better than the other case and the connection is perfect. In a certain sense these cells are intermediate between the rod cells and those that supply the pericellular meshwork. (Fig. 25.)

Dogiel[1] has shown that in the eyelids of man, for example, where the number and complexity of the sense organs is extreme, the terminal bodies consist of a covering of several connective tissue layers separated by zones of flat epithelial cells enclosing the nerve net. The nerve net is described as lying free in the interior of the bulb, though a faintly stained material was noticed and regarded as coagulated lymph which may represent cellular elements not competent to be revealed by the methylene blue method. (Fig. 9.) The nerve fiber loses its sheath before it penetrates the bulb and at once divides into spirals or coils forming a loose mesh-work. Aside from these specific cells, there are extensive arborizations and nets of fibers diffusely scattered in the epithelium at large.

In some respects the fullest description of the highly differentiated sense organs of the skin of the genitalia has been given by Dogiel and his results are pertinent to our purpose, inasmuch as he finds that all the end-organs reduce to one type—a terminal recticulum. The so-called genital sense organs and the Krause's and Meissner's bodies all prove to consist of a capsule containing a reticulum of varicose fibers and, especially in the case of the genital corpuscles, those of the same order are frequently connected by lateral anastomoses. In addition to these special organs, Dogiel traces medullated fibers into an inter-cellular reticulum within the epithelium so fine and dense as to come apparently into relations with all the cells of the deeper parts of this layer. Occasionally a branch turns peripherally and ends in a knob at some distance below the surface. We seem, then, to have evidence that the typical form of nerve ending is a close pericellular network, though Dogiel's method is not such as to allow of determining the relation of the fibers to the cells. (Fig. 1.)

The most remarkable suggestion respecting the homologies of the sense organs of the skin in amphibians is that of Maurer who thinks that the hair of vertebrates can be traced back phy-

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[1] A. S. DOGIEL. Die Nervenendigungen i. Lidrande, etc. Archiv f. Mik. Anatomie, XLIV, 1, 1894.

logenetically to these sense organs. Leydig in Biolog. Centralblatt, XIII, scouts this idea and derives the hair from the so-called "Perlorgan" of certain fishes. The resemblance and affinity of the sense organs is rather with the auditory apparatus, as shown by Ayers and others.

The Sense Buds. It is interesting to observe the wide differences of opinion of competent observers as to the endings in the end buds. Lenhossèk (Anat. Anzeiger, VIII, 4) denies absolutely Fusari and Panisci's statement that the proximal extremity of the sensory cells in the taste bud passes directly into a nerve fiber and states that the nerves always end free in the bud, or rather form a meshwork surrounding it, thus constituting a peri-gemmal reticulum. Nerve fibers pass in a horizontal course below the epithelium and give off collaterals from time to time which form a felting of free fibers among the general epithelium cells. Essentially similar conditions prevail in the sense buds of the mouth of fishes and the author concludes that the rod cells are to be considered as short apolar nerve-cells and that the class of nerve endings found in the earth-worm is found in vertebrates only in the olfactory organ. (Figs. 15 and 16.) Retzius takes the same view, but finds that the nerve fibers are not perigemmal but intragemmal, thus illustrating the difficulties growing out of a reliance on the Golgi and methylene blue methods alone.

A. Geberg in a brief article in the Anat. Anzeiger, VIII, 1, claims to be able to demonstrate the endings of the auditory nerve in the cochlea by the methylene method, but, inasmuch as the tissues were not stained, it seems that his conclusion, that the fibers attach themselves to the hair cells without communicating with the latter, must be considered as non-conclusive.

Having reinvestigated the nerve endings in the sensory buds of the skin of the axolotl with material leaving little to be desired as to the fixation and hardening, and which had been double stained successfully, we are able to assert with great confidence that, in this case, there is a special cellular nerve terminus having a direct basal connection with a nerve fiber. The nucleus of these cells (which cannot be termed appropriately rod cells or "Stiftzelle") is narrower and more deeply stained than the supporting cells and occupies the entire width of the cell. The peripheral part of these cells has not been correctly described as yet. In reality it consists of a projection of the cell walls to form a narrow tube. These walls are delicate and very thin but easily seen because of the contrast with the protoplasmic fiber contained in it. The latter structure is delicate but stains a deep red with the picrocarmine, while the walls are not stained by that reagent. (Figs. 26-30.) This axial fiber differs not at all from that seen in the clusters found in the scattered sense organs on the head of the tree frog and the frog. (Fig. 32.) The proximal portion of the cell is not as easy to trace, for the corium and often the chromatophores obscure the connections to a degree. Yet it now and then happens that the direct communication with a nerve fiber rising through the corium can be made out. Of course it may be insisted that this connection is only a secondary one, but nothing but evidence from embryology or degeneration experiments will substantiate or refute the claim. So far as the evidence now goes, the scattered cells above mentioned and those in the buds stand or fall together, and for the former the evidence of direct continuity between cell and nerve is unimpeachable.

The Plexus Beneath the Corium.—In portions of the skin stained *intra vitam* by the methylene blue method and examined at once in glycerine very perfect views of the marvelously elaborate plexus beneath the corium can be gained. The fibers are of two sorts, the larger being connected with the fibers from the nerve bundles from the central system, while a part at least of the fibers of smaller calibre have a local origin in certain ganglion cells of this region. These cells were first detected in preparations double-stained with hæmatoxylin and picrocarmine and were seen in section in a plane parallel to the surface. In the methylene blue preparations they are very conspicuous and surprisingly numerous. The nuclei are large, while the protoplasm of the cell does not stain or only slightly with the blue. It is an interesting and most instructive fact that the cell body remains transparent, while its own neurite or axis cylinder process is mostly intensely stained through its entire length. The hiatus between the fiber and its cell is slight but sufficient to cast a doubt on the fact of communication were the conditions not absolutely favorable. With a high power it is possible to see the sheath and the faintly tinged protoplasm so that no doubt is in this case possible.

It may be noted also that other methods seem to show that it is entirely possible for the protoplasm of a cell to react differently from that of the axis cylinder derived from it. Thus may be explained many of the ambiguous and conflicting results of the applications of the methylene blue process. Fig. 33 illustrates the appearance of a section stained with hæmatoxylin and picrocarmine, while Fig. 23 is from a methylene blue preparation. Figs. 33-37 are from surface views of the plexus, showing the ganglion cells. Figs. 38 and 39 are from the same region, showing connections with vessels and chromatophores (Fig. 3.)

It will be seen that the fibers of this plexus below the corium are of two sorts. The fine fibers arise, in part at least, in the local ganglion cells and can be traced to the nerve bundles, which they enter and then mingle with the fibers of the larger sort. In the perpendicular sections it is easy to see that a certain number of fibers from the general "mixed" nerves pass without interruption into the skin and so do not participate in the formation of the plexus. Others, on the other hand, divide dichotomously in the level of the plexus and the branches give off "collaterals" that pass through the corium and so reach the epithelial layer. It is not possible to state positively that fibers from the ganglion cells of the plexus give off fibers to the skin, though such certainly is the appearance. After passing through the corium, the fibers do not all at once seek out their definite termini in the cells of the epithelial layer, but they often turn sharply at right angles at the ectal surface of the corium and pass long distances parallel to the surface. This tendency is more marked in some regions than in others. This fact greatly complicates the study of the endings. In the case of taste buds and the organs of the lateral line this is one of the most serious difficulties in the way of a correct interpretation of the appearances presented by sections.

A discussion of the theoretical bearings of these facts and further details must be deferred to the second part of this paper.

Since writing the above we have been able to settle several points previously in doubt. None of our preparations of the skin of amphibians gave unambiguous results for the glands of the skin. We have at last succeeded in securing excellent *intra vitam* impregnations in the toad (Bufo sp.) in which it is easy to trace the non-medulated fibers from the plexus ectad of the corium, and also from that entad of it, into the most intimate connection with the superficial walls of the glands, which in this species are very large and highly functional. The fibers are of small caliber but are excessively numerous and envelop the whole gland in what at first looks like a closely woven reticulum, but a close study shows that the appearance of a reticulum is due to the repeated dichotomous branching of a large number of distinct nerve fibers. These fibers cross at slightly different levels and there is no doubt in most cases of the complete distinctness of the fibers as they cross. Upon these fibers are frequent varicosities which may be due to imperfections of the process or may be the points of attachment of the fibers upon the cells of the gland. Of course this method does not admit of determining the exact relation of the nodosities to the several cells, but there can be no doubt of the existence of a very intimate and necessary connection. One is forcibly struck by the close resemblance of this periglandular felting to the perigemmular reticulum described by many authors in the case of the sense buds. The latter is, as we have before insisted, entirely distinct from and totally unlike the intragemmular endings in distinct cells which may be demonstiated by a wide range of independent methods.

The same preparations used in the earlier parts of this paper have also afforded to a more extended study a number of satisfactory views of the connection of the ganglion cells of the reticulum below the corium with fibers—not only with such as pass directly into the nerve bundles but, as we now find, with with non-medullated fibers which pass through the corium and end in relation with the cells of the epithelium layer. We also find that these and other fibers, after passing through the corium, turn and pass for long distances parallel to the surface to their final destination in the upper layer. This seems to be particularly true of the fibers of the perigemmular series of the sense buds. In some cases well defined bundles of nerves in a common sheath pass through the corium, while in those cases where the nerve sheath is present it is soon lost after passing the corium. It seems natural to conclude that the non-medullated fibers of the epithelium are essentially similar to the fibers of the same structure that supply the glands. If so, we may add that these are in both cases centrifugal and we have a suggestisn at least toward the solution of the puzzle as to the respective functions of the several classes of fibers. That the general cells of the skin have more or less power of absorption and excretion, as well as secretion, can hardly be doubted and, if so, why may not these fibers from the disperse ganglia of the peripheral sympathetic system be the neural sponsors for these functions? The methylene blue method reveals the same sensory endings in the skin that we have described fully from histological preparations, but curiously enough they appear as fibers simply because the nuclei are not stained and this fact explains the discrepancy in the two methods.

It is interesting to compare the intercellular net-work described above with the similar so-called connective tissue network described by Bruyne (Arch. de Biol., XII, 1892) surrounding the muscle fibers. The figure given in the article by the same author in Anat. Anzeiger, X, 18, is so remarkably similar to the apearance we have called attention to that one may be pardoned for suspecting similarity of nature. It may be that more than one instance of intercellular bridges rests on the misinterpretation of similar structures. The relation of the space so kept open between the cells to the circulatory fluid is a question of greater interest than seems to have been suspected.

NOTE ON THE METHYLENE BLUE PROCESS. It appears that we have had in one respect the usual experience with the methylene blue *intra vitam* impregnation process. It is not difficult to secure excellent impregnations of the nerves of the skin of the Amphibia in which the nerve fibers are deeply and quite selectively stained, yet it appears that there is a strong tendency for the stain to be extracted or rendered diffuse by the process of imbedding so that tissues which were very perfectly stained in the glycerine are quite unsatisfactory in thin section. It appears that the difficulty is in the action of the alcohol, which is required in both the paraffin and the celloidin methods of imbedding. To obviate this difficulty we have resorted with good results to the use of a mixture of gum arabic and glycerine. The fragment is placed in glycerine or may be placed at once in the gum-glycerine. After an impregnation of a day or two in a closed bottle the specimen is mounted in a paper tray with the mixture and the latter is allowed to evaporate till a consistency is reached which will permit it being placed in the microtome and sectioned. In this way sections are secured thin enough to serve the pupose desired and these may be mounted in gum-glycerine or may then be dissolved out of the gum and treated in any way desired.

EXPLANATION OF FIGURES.

PLATE V.

Fig. 1. Diagram of the skin of the sexual organs, after Dogiel.

Fig. 2. End-organs in the skin of the tree frog, original. Teased preparation.

Fig. 3. Sense bud of young salamander. Original.

Fig. 4. Skin of tadpole with nerve endings and the transitory skeins interpreted as nerve endings by Pfitzner.

Fig. 5. Skin of very young tadpole. Original.

Fig. 6. Skin of tadpole, near angle of mouth, Original.

Fig. 7. Sense bud of Amblystoma. Original.

Fig. 8. Nerve endings in the epithelium of the frog, according to Bethe.

A.—"Gabelzelle," from sensory papillæ of tongue.

B.—Cylinder cells.

C.—Isolated rod cell.

D.—Upper part of papilla.

E.—Ciliate cell of palate.

Fig. 9. Nerve ending in the human conjunctiva. Dogiel.

Fig. 10. Nerve endings in Jacobson's organ. Lenhossèk.

Fig. 11. Nerve endings in the taste buds. Arnstein.

PLATE VI.

Fig. 12. Section from the skin of the head of a tree-toad. *a*, nerve bundle and endings; *b*, gland; *c*, corium; *d*, small gland; *e*, chromatophore.

Fig. 13. Skin of head of leopard frog showing cellular nerve endings in groups penetrating the skin.

Fig. 14. Similar endings from the tree frog.

Figs. 15, 16. See Plate VIII.

Fig. 17. Part of the skin of the axolotl showing the nerve bundle on its way to the skin and the pericellular net-work.

Fig. 18. Skin of axolotl showing pericellular net-work and the nerve-fibers entering from below.

Fig. 19. Similar section fixed in Flemming's solution.

Fig. 20. A section of portion of axolotl skin where the Leydig cells (*L. c.*) are two-layered. Proliferating cells (*k*) in lower series of protoblasts; *c*, corium; *B. V.*, capillary; nerve fibers entering from below.

Figs. 21-23. See Plate VIII.

Fig. 24. Skin of tadpole as figured by Pfitzner.

PLATE VII.

Fig. 25. Section from a different part of the skin with cellular nerve termini. This is probably to be explained as the result of the elongation of the basal series of the epithelial cells.

Fig. 26. Sensory bud from skin of axolotl, showing the tubular peripheral ending of sensory cells with fine thread of protoplasm extending to periphery and the basal connective with nerves.

Fig. 27. Sensory bud from another part of skin.

Fig. 28. Similar bud in which the peripheral portion of the sensory element seems divided. Explained as due to the shrinkage and "fraying out" of the wall.

Fig. 29. See Plate VIII.

Fig. 30. Isolated supporting cells from specimens similar to Fig. 28, stained with hæmatoxylin, picro-carmine and methylene blue. Are the blue fibers nerves, or are they lines of precipitation in folds of the cell wall due to shrinkage? Compare Fig. 11.

Fig. 31. Cells from nasal cavity of leopard frog.

Fig. 32. Nerve endings from skin of same to illustrate similarity to the last.

Fig. 33. Skin of gills of axolotl to show ganglion cells beneath the corium.

PLATE VIII.

Fig. 15. Pericellular nerve fibers from sensory bud of conger eel.

Fig. 16. Intrabulbar endings in *Barbus*. (Both 15 and 16 from Lenhossèk.)

Fig. 21. Skin of the axolotl showing nerve endings in or near the chroma tophores and in the skin of the axolotl. Methylene blue.

Fig. 22. Similar to Fig. 21, showing endings in layer of protoblasts.

Fig. 23. Perpendicular section through skin of axolotl stained *intra vitam* with methylene blue and cleared in glycerine. The plexus beneath the corium. is clearly visible.

Fig. 29. Cells similar to to Fig. 28, stained with methylene blue.

Fig. 34. Surface view of methylene blue preparation, similar to Fig. 33, showing connection of ganglion cells with nerve bundles.

Fig. 35. Same as Fig. 34.

Figs. 36, 37. Ganglion cells of large ramose form from same layer as above.

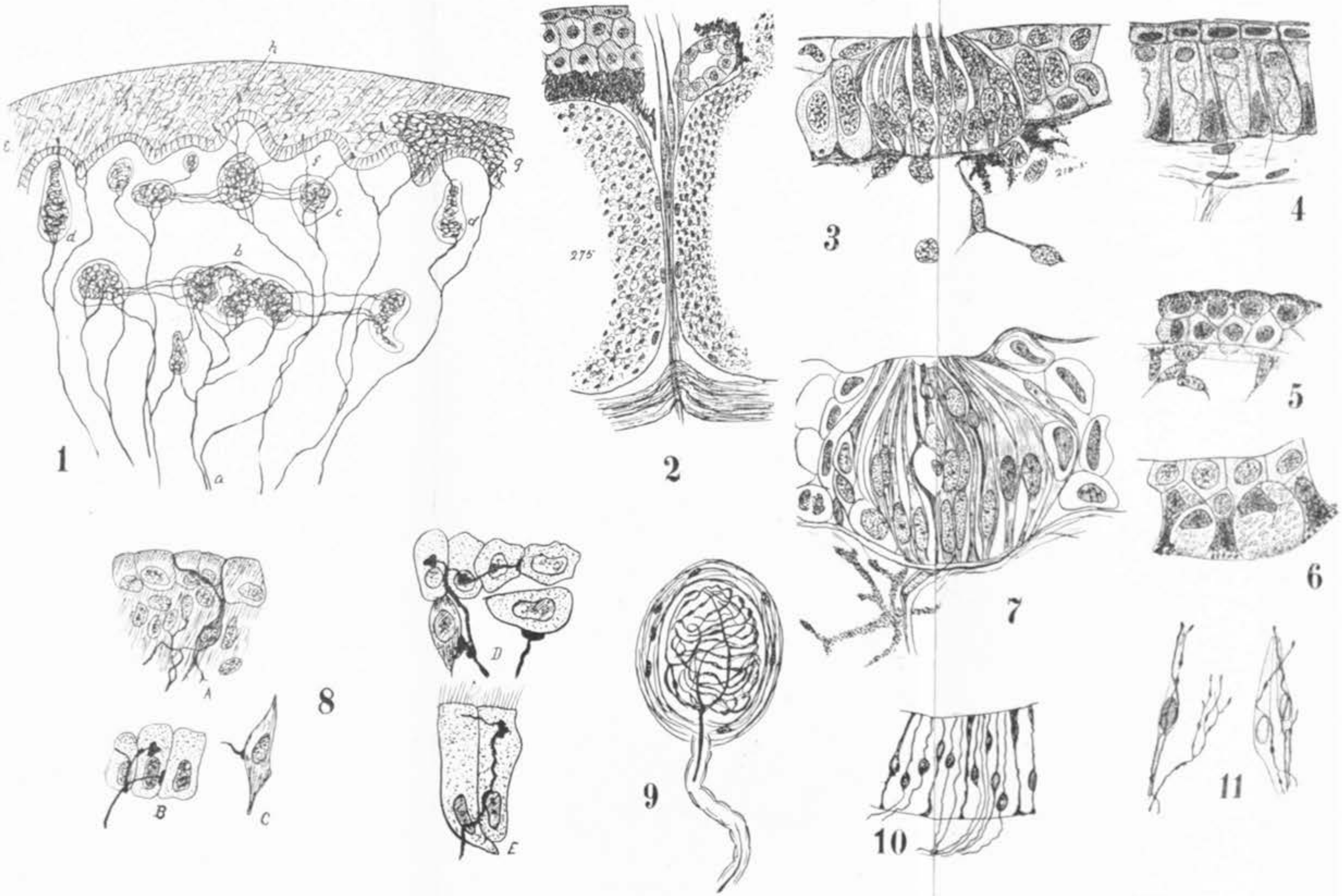
Fig. 38. Relation of nervous reticulum below the corium to the capillaries.

Fig. 39. Chromatophore-like ganglion cells.

PLATE IX.

Fig. 40. Section of the skin of the head of a toad (Bufo) after *intra vitam* injection with methylene blue and fixation with Bethe's solution of molybdate of ammonia. Examined in glycerine. The section is somewhat oblique so that the duct and part of the body of the gland is removed. The delicate non-medulated fibers are seen generously distributed over the uncut surface of the gland. Coarser fibers are also seen in the lower and upper plexuses, also a bundle of sensory rods at the left.

Fig. 41. Intra vitam methylene blue preparation of skin of axolotl, showing connection of cells of the ganglionic meshwork beneath the corium with the epidermis. *a*, fiber passing to cells of the intracellular reticulum; *b*, non-medullated fibers from a nerve piercing the corium; c, c^1, c^2 and c^3, ganglion cells of the plexus beneath the corium.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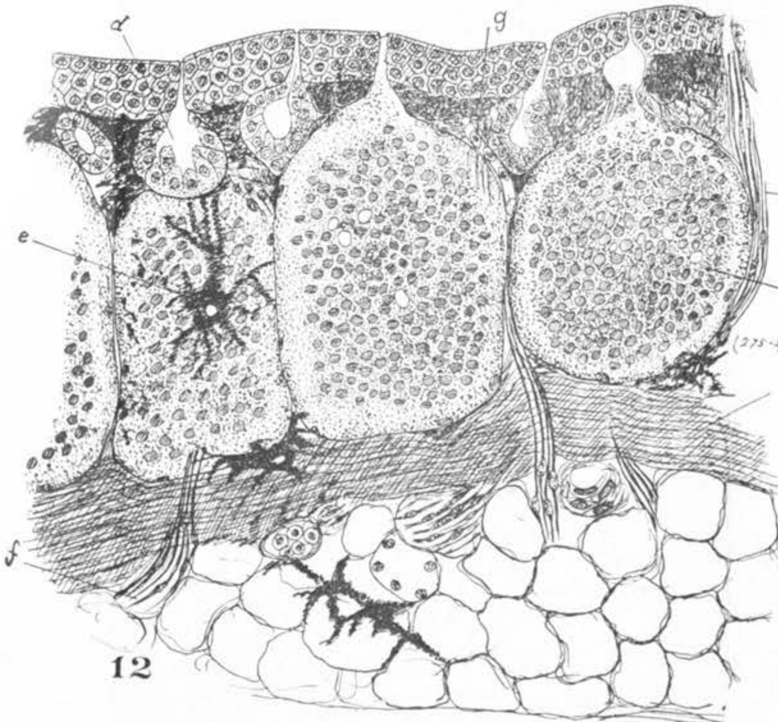

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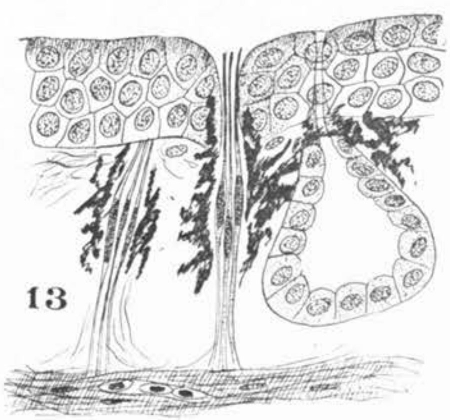

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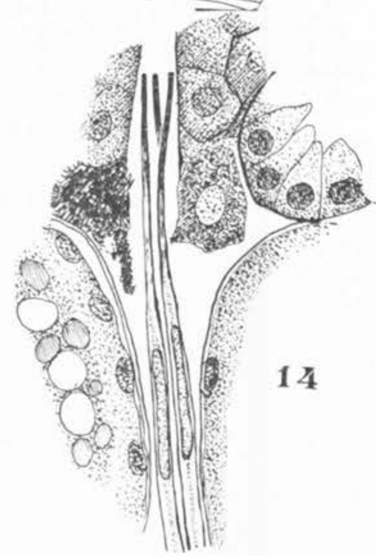

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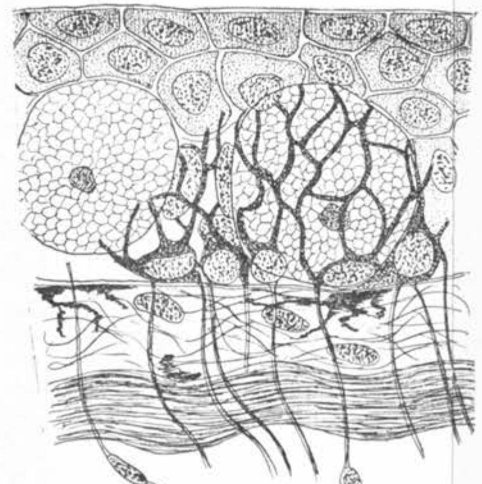

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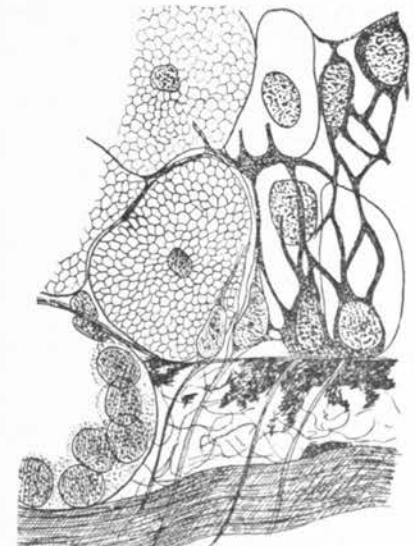

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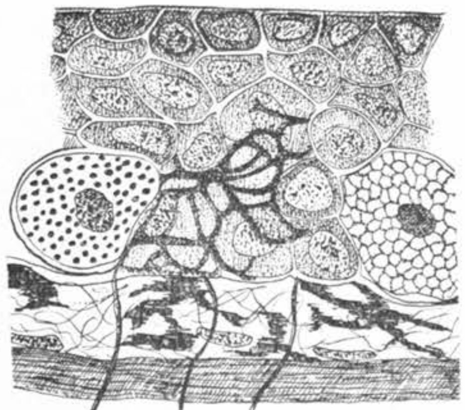

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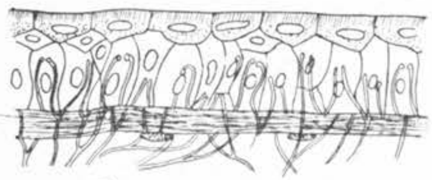

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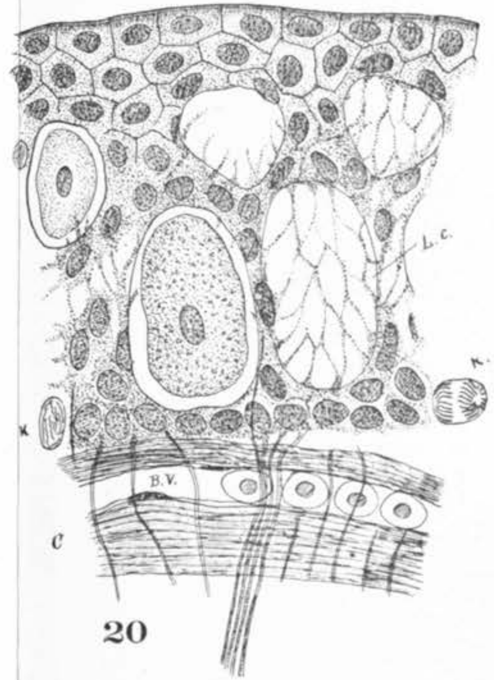

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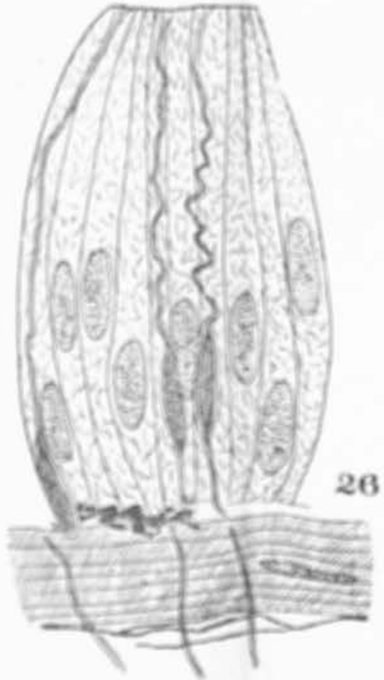

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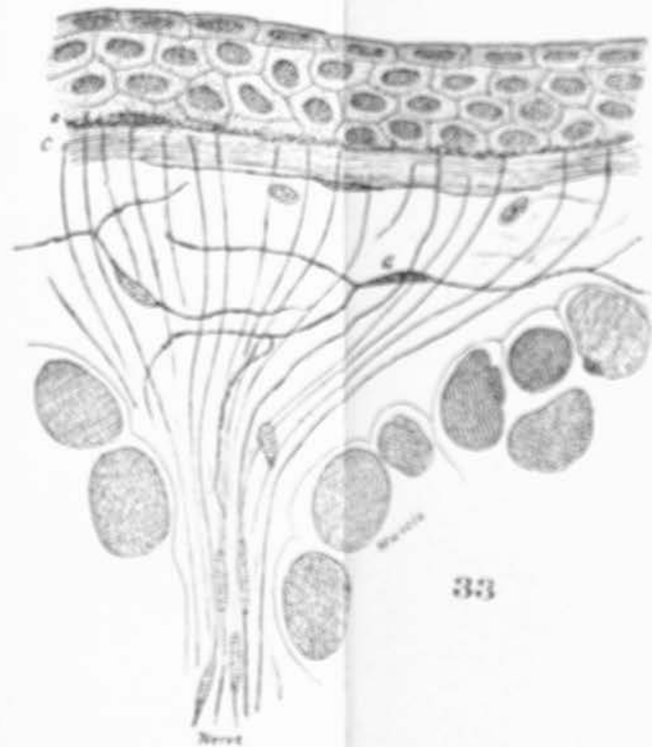

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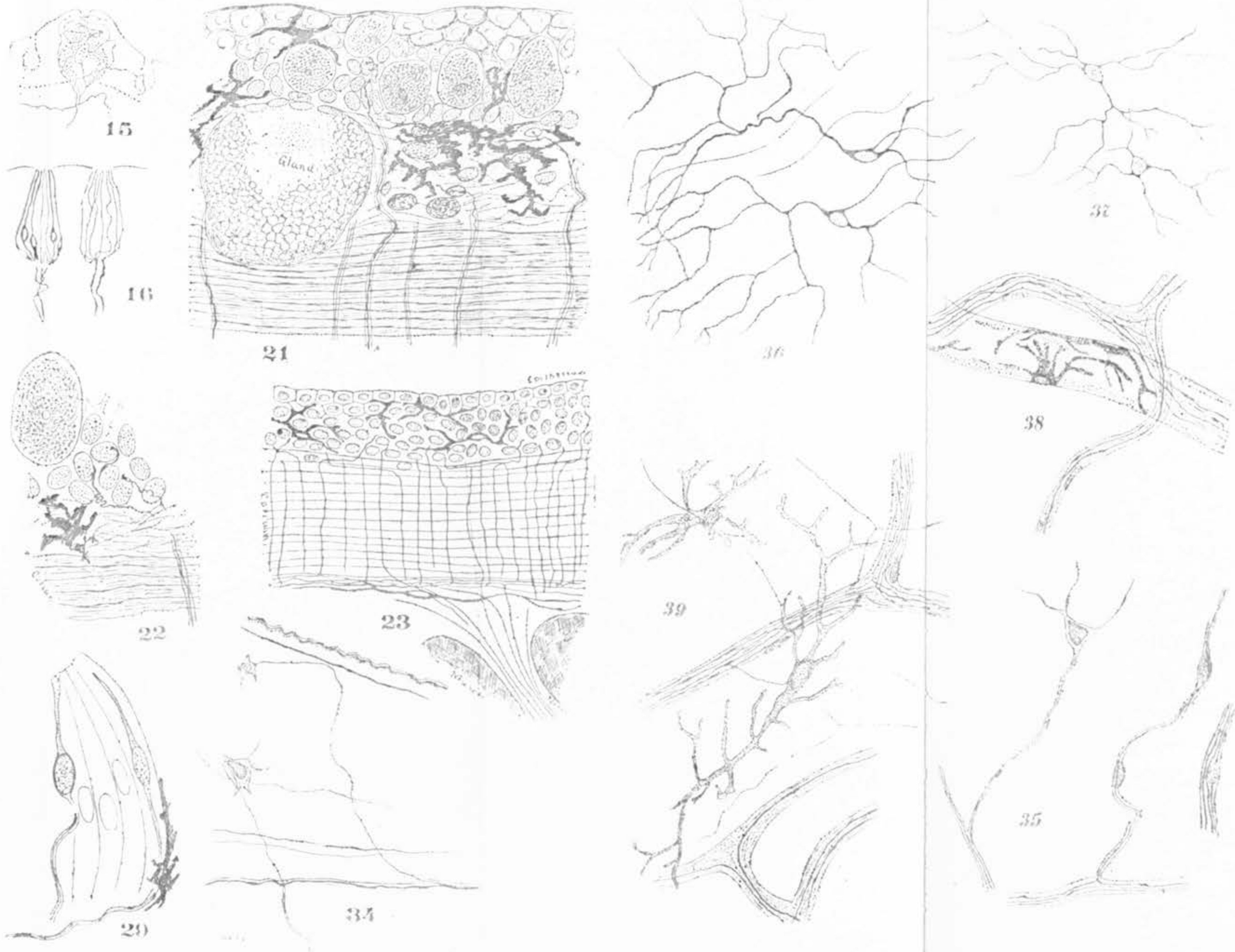
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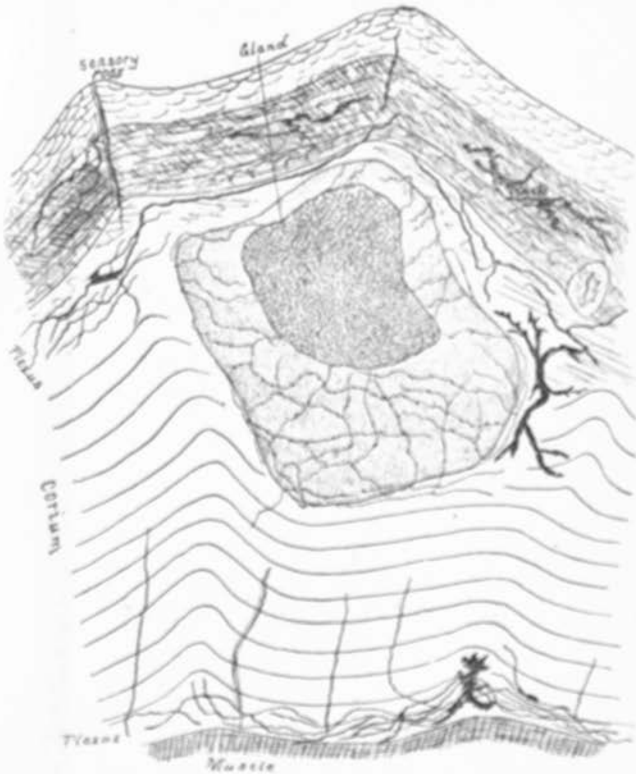

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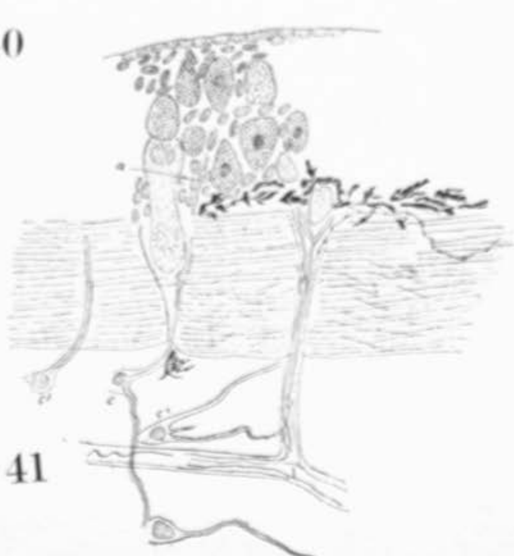

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